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(54) Title: USE OF FLIBANSERIN IN THE TREATMENT OF SEXUAL DISORDERS

(57) Abstract: The invention relates to the use of flibanserin for the preparation of a medicament for the treatment of disorders of sexual desire.



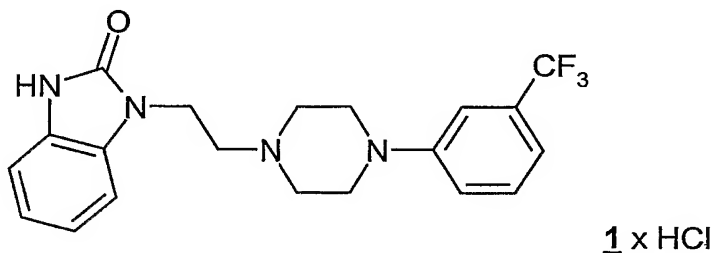
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USE OF FLIBANSERIN IN THE TREATMENT OF SEXUAL DISORDERS

The invention relates to the use of flibanserin for the preparation of a medicament for the treatment of disorders of sexual desire.

Description of the invention

The compound 1-[2-(4-(3-trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one (flibanserin) is disclosed in form of its hydrochloride in European Patent Application EP-A-526434 and has the following chemical structure:



Flibanserin shows affinity for the 5-HT_{1A} and 5-HT₂-receptor. It is therefore a promising therapeutic agent for the treatment of a variety of diseases, for instance depression, schizophrenia, and anxiety.

In studies of male and female patients suffering from sexual dysfunction it has been found that flibanserin optionally in form of the pharmacologically acceptable acid addition salts thereof displays sexual desire enhancing properties. Accordingly, the instant invention relates to the use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of disorders of sexual desire.

In a preferred embodiment the invention relates to the use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of disorders selected from the group consisting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire, loss of libido, libido disturbance, and frigidity.

Particular preferred according to the invention is the use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of disorders selected from the group consisting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire.

In a particularly preferred embodiment the invention relates to the use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of disorders selected from the group of Hypoactive Sexual Desire Disorder and loss of sexual desire.

The observed effects of flibanserin can be achieved in men and women. However, according to a further aspect of the invention the use of flibanserin optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of female sexual dysfunction is preferred.

The beneficial effects of flibanserin can be observed regardless of whether the disturbance existed lifelong or was acquired, and independent of etiologic origin (organic - both, physically and drug induced-, psychogen, a combination of organic - both, physically and drug induced-, and psychogen, or unknown).

Flibanserin can optionally used in form of its pharmaceutically acceptable acid addition salts. Suitable acid addition salts include for example those of the acids selected from, succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid and citric acid. Mixtures of the abovementioned acid addition salts may also be used. From the aforementioned acid addition salts the hydrochloride and the hydrobromide, particularly the hydrochloride, are preferred.

Flibanserin, optionally used in form of its pharmaceutically acceptable acid addition salts, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, aqueous or non aqueous vehicles, polyvinyl pyrrolidone, semisynthetic glycerides of fatty acids, benزالconium chloride, sodium phosphate, EDTA, polysorbate 80. The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. The dosis range applicable per day is between 0.1 to 400, preferably between 1.0 to 300, more preferably between 2 to 200 mg. Each dosage unit may conveniently contain from 0,01 mg to 100 mg, preferably from 0,1 to 50 mg.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. of a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. of. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

The Examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
	flibanserin hydrochloride	100 mg
	lactose	240 mg
	corn starch	340 mg
	polyvinylpyrrolidone	45 mg
	magnesium stearate	15 mg
		<hr/>
		740 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per tablet</u>
	flibanserin hydrochloride	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	<u>2 mg</u>
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

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C)	<u>Coated tablets</u>	<u>per coated tablet</u>
	flibanserin hydrochloride	5 mg
	corn starch	41.5 mg
	lactose	30 mg
	polyvinylpyrrolidone	3 mg
	magnesium stearate	<u>0.5 mg</u>
		80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

D)	<u>Capsules</u>	<u>per capsule</u>
	flibanserin hydrochloride	1 50 mg
	Corn starch	268.5 mg
	Magnesium stearate	<u>1.5 mg</u>
		420 mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E) Ampoule solution

flibanserin hydrochloride	50 mg
sodium chloride	50 mg
water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered

free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion.

F) Suppositories

flibanserin hydrochloride	50 mg
solid fat	<u>1650 mg</u>
	1700 mg

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

Patent Claims

- 1) Use of flibanserin, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of disorders of sexual desire.
- 2) Use according to claim 1, characterized in that the disorder of sexual desire is selected from the group consisting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire, loss of libido, libido disturbance, and frigidity.
- 3) Use according to claim 1 or 2, characterized in that the disorder of sexual desire is selected from the group consisting of Hypoactive Sexual Desire Disorder, loss of sexual desire, lack of sexual desire, decreased sexual desire, inhibited sexual desire.
- 4) Use according to claim 1 for the preparation of a medicament for the treatment of female sexual dysfunction.
- 5) Use according to one of claims 1, 2, 3 or 4, characterized in that flibanserin is applied in form of a pharmaceutically acceptable acid addition salt selected from the salts formed by the acids selected from, succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid, citric acid, and mixtures thereof.
- 6) Use according to one of claims 1 to 5, characterized in that flibanserin is applied in a dosis range between 0.1 to 400 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/496 A61P15/00 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 526 434 A (BOEHRINGER INGELHEIM ITALIA) 3 February 1993 (1993-02-03) cited in the application claim 3 page 3, line 25-29 ---	1-6
X	WO 01 21593 A (BOEHRINGER INGELHEIM ITALIA ;SCHIAVI GIOVANNI BATTISTA (IT); CERED) 29 March 2001 (2001-03-29) claims 1-14 page 1, line 34-39 --- -/--	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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- *&* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>RUETER L E ET AL: "Electrophysiological examination of the effects of sustained flibanserine administration on serotonin receptors in rat brain." BRITISH JOURNAL OF PHARMACOLOGY. ENGLAND FEB 1999, vol. 126, no. 3, February 1999 (1999-02), pages 627-638, XP009003002 ISSN: 0007-1188 abstract</p> <p>-----</p>	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/11103

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0526434	A	03-02-1993	IT 1251144 B	04-05-1995
			AT 191910 T	15-05-2000
			AU 665366 B2	04-01-1996
			AU 2427592 A	02-03-1993
			CA 2114542 A1	18-02-1993
			CZ 281511 B6	16-10-1996
			CZ 9400170 A3	18-05-1994
			DE 69230926 D1	25-05-2000
			DE 69230926 T2	05-10-2000
			DK 526434 T3	17-07-2000
			EE 3070 B1	16-02-1998
			EP 0526434 A1	03-02-1993
			ES 2144412 T3	16-06-2000
			FI 940420 A	28-01-1994
			GR 3033947 T3	30-11-2000
			HK 1010725 A1	12-01-2001
			HU 70195 A2	28-09-1995
			HU 9500292 A3	28-09-1995
			IE 922464 A1	10-02-1993
			IL 102665 A	31-10-1996
			WO 9303016 A1	18-02-1993
			JP 6509575 T	27-10-1994
			KR 263495 B1	01-11-2000
			MX 9204139 A1	01-01-1993
			NO 940306 A	14-03-1994
			NZ 243777 A	27-04-1995
			PL 302163 A1	11-07-1994
			PT 526434 T	31-08-2000
			RU 2096411 C1	20-11-1997
			SG 52407 A1	28-09-1998
			SK 10194 A3	07-12-1994
			US 5576318 A	19-11-1996
			ZA 9205682 A	31-01-1994
WO 0121593	A	29-03-2001	IT MI991964 A1	22-03-2001
			AU 7653700 A	24-04-2001
			WO 0121593 A1	29-03-2001
			EP 1218352 A1	03-07-2002
			US 6281218 B1	28-08-2001